

REMARKS

I. Claim Amendments

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claim 23 has been amended to further prosecution of the application. In particular, claim 23 has been amended to incorporate the limitations of claims 12, 13, and 15. As such, claims 12, 13, and 15 are requested to be cancelled without prejudice. Because the foregoing amendments are fully supported by the claims and application as filed, entry is respectfully requested. After entry of the foregoing amendments, claims 14, 16-20, and 23-25 are pending in the application.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. Claim Rejections - 35 U.S.C. § 103

In the Office Action, Claims 23-25 and 12-20 were rejected under 35 U.S.C. § 103 as being unpatentable over Kamada *et al.* (U.S. 5,384,130) in view of Menzi *et al.* (U.S. 6,056,949) and Makino *et al.* (U.S. 5,026,560). Applicants respectfully traverse the rejection.

Claim 23 is the only independent claim in the application. The cited references, either alone or in combination, do not teach or suggest the method recited in claim 23 comprising the limitations recited in a), b), c), and d). In particular, none of the references teach or suggest a method that uses organic solvent at a concentration of 5 – 25% (wt.). As noted in the specification: “The process according to the invention advantageously makes it possible to limit the quantity of organic solvent used. During the process of the invention, 5 to 25% by weight of organic solvents are used.” *See* specification at page 9, paragraph [0042]. In

addition, the disclosed Examples recite the use of alcohol. *See id.* at pages 11-15, Examples 1-5.

In contrast, Kamada *et al.* teach a method that does not utilize organic solvent at all. Rather, Kamada *et al.* teach the use of solvent-free aqueous suspensions. *See, e.g.,* Kamada *et al.*, col. 5, lines 42-57. Further, Kamada *et al.* indicate that the use of an organic solvent is undesirable and should be replaced by aqueous suspensions.

In many cases where seed cores are coated with powder containing active ingredients, an organic or aqueous solution of a binder is used as a binder solution. When a coating is applied, a solution of a coating agent in an organic solvent is used. ***The use of an organic solvent brings problems relating to environmental pollution, cost, residues and the like.*** Thus, ***these organic solvents will be gradually replaced by aqueous solutions or suspensions.***

Id., col. 2, lines 3-11 (emphasis added). Therefore, Kamada *et al.* teach away from the presently claimed method and one skilled in the art would not rely on the teachings of Kamada *et al.* to perform the presently claimed method.

Moreover, one skilled in the art would not be motivated to combine the three (3) references cited by the Examiner to render obvious the method of claim 23. Kamada *et al.* indicate that the “problem to be solved” relates to the use of aqueous solutions when preparing “seed cores composed of sucrose or sucrose/starch...coated with a powder containing an active ingredient.” Kamada *et al.* state:

Nevertheless, in a process for the preparation of a pharmaceutical wherein seed cores composed of sucrose or sucrose/starch are coated with a powder containing an active ingredient, using a binder aqueous solution, and further coated by spraying an aqueous solution or suspension of a coating agent, certain problems arise. For example, sucrose, which is a main ingredient of the seed cores, is dissolved, the surface of the seed cores becomes tacky, and the seed cores exhibit a high friability. These problems cause disadvantages, such as aggregation of granules, adhesion of granules to a wall of a coating machine, and a lowered yield. Moreover, the resulting granules have a problem in that the dissolution rate of the active

ingredient from the granules is lowered with the passage of time. Further, upon administration, since sucrose, a main ingredient of the seed cores, is gradually dissolved. This results in a reduction of the strength of the granules. An intestinal movement may therefore break the coating of the granules. Since this coating is intended to control the dissolution of the active ingredient, a highly undesirable dissolution profile may appear.

Id., col. 2, lines 12-34. To address the stated problem, Kamada *et al.* teach the use of “spherical seed cores containing **at least 50% of microcrystalline cellulose.**” *Id.*, col. 2, lines 36-39 (stating that “[t]he present inventor surprisingly found that the various above-mentioned problems can be resolved by providing pharmacologically inactive spherical seed cores containing at least 50% of microcrystalline cellulose”)(emphasis added).

Convention seed cores such as “Nonpareil” are not suitable for the method of Kamada *et al.* See *id.* at col. 12, lines 8-21 (stating that “seed cores [of the invention provide] granules wherein the aggregation is reduced to one tenth of that of granules using conventional seed cores such as Nonpareil and the yield is increased by 5% compared with granules using conventional seed cores.”) In addition, comparative Examples disclosed by Kamada *et al.* indicate that Nonpareil-101 and Nonpareil-103, when compared to seed cores that included microcrystalline cellulose, provided seed cores that “dissolved” (see *id.*, col. 11, Table 5), and that exhibited a higher “Degree of aggregation (%)” and a lower “Yield (%)” (see *id.*, col. 11-12, Tables 6-8). As such, Kamada *et al.* indicate that Nonpareil-101 and Nonpareil-103 provided unsuitable seed cores and teach away from the use of Nonpareil.

Therefore, based on the teachings of Kamada *et al.*, there is no motivation to combine Kamada *et al.* with any reference that teaches the use of an organic solvent or that teaches the use of seed cores that do not include “at least 50% of microcrystalline cellulose,” (e.g., Nonpareil seed cores). Despite this, the teachings of Kamada *et al.* are combined with Makino *et al.* to provide support for the following propositions:

Makino is used to show the ***typical ranges of sucrose and starch in a neutral core***. Makino teaches methods of preparing coated granules comprising a neutral core coated with any suitable active substance including nutritional substances....The core used by Makino is a ***nonpareil produced by 75% sucrose and 25% starch***....The core can be coated with any drug substance and an excipient/binder such as PVP.

See Office Action dated June 7, 2005, at page 4 (citations omitted). However, as noted above, Kamada *et al.* teach away from the use of Nonpareil-101 and Nonpareil-103 or any seed core that does not include “at least 50% of microcrystalline cellulose.” Therefore, it is improper to combine Kamada *et al.* with Makino *et al.* to obtain support for the proposition of using a nonpareil neutral core that includes sucrose and starch as indicated in the rejection under 35 U.S.C. § 103. One skilled in the art would not be motivated to apply the teachings of Kamada *et al.* to the teachings of a reference related to Nonpareil to perform the presently claimed method.

Likewise, one skilled in the art would not be motivated to combine the teachings of Kamada *et al.* with Menzi *et al.* First, Menzi *et al.* teach the use of organic solvent. As indicated by the Examiner, Menzi *et al.* teach “water and ethanol as their solvent of choice.” See Office Action dated June 7, 2005, page 4, (citing Menzi *et al.*, col. 2, lines 28-30). Moreover, Menzi *et al.* do not teach seed cores that include “at least 50% of microcrystalline cellulose.” Therefore, one skilled in the art would not be motivated to combine the teachings of Kamada *et al.* with Menzi *et al.* to perform the presently claimed method.

Therefore, for all these reasons, the claimed method is not obvious in view of the cited references. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

III. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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